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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,455	06/01/2006	**Michal Amit**	32059	2318

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
07/30/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,455	AMIT ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52,55,57-75 and 78-101* is/are pending in the application.

4a) Of the above claim(s) *61-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,55,57-60,74,75 and 78-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/13;5/30*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 6/29/10, has been entered. Claims 52, 55, 57-75, 78-101 are pending; claims 61-73 are withdrawn; claim 101 is newly added; claims 52, 55, 57-60, 74, 75, 78-101 are under current examination.

Information Disclosure Statement

Applicants' IDS, filed 5/13/10 and 5/30/10 have been considered.

Election/Restrictions

Claims 61-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/28/08.

Applicant's election of Group I (claims 52, 55-60, 74-74, 78-84) in the reply filed on 11/28/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants further elected SEQ ID NO: 34 for a species election. The Examiner withdraws the species restriction requirement and all species are examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52, 55, 58-60, 74, 75, 78-80, 85, 86, 88-94, 99, 100 and newly added claim 101 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* (**Science**, 282: 1145-1147, November 6, 1998, cited previously) in view of Harper (**J. of Assisted Reproduction and Genetics**, 13(2): 90-95, 1996) in further view of US Pat. No. 7,390,659 (Issued June 24, 2008, cited previously) and Elsea *et al.* (**ILAR Journal**, 43(2): 66-79, 2002, cited previously).

Applicants' Arguments. Applicants argue that Thomson teaches generating human ES cell lines from normal human embryos, not embryos which carry naturally occurring disease-causing mutations, as in the claimed invention. Additionally, Thomson teaches genetic modifications that are not relevant to the instant claims because they are non-natural modifications, not naturally occurring mutations. See pages 11-12 of the Response.

Applicants further argue that Harper teach pre-implantation diagnosis to select for normal embryos *i.e.,* devoid of mutations, which are further implanted back into the uterus for continuation of normal embryonic development in order to achieve the birth of healthy offspring, and that it is inferred from Harper that embryos carrying disease-causing mutations should be discarded, and further do not teach or suggest using the genetically abnormal embryos for any purpose, and

teaches away from the claimed invention in that they infer discarding those genetically abnormal embryos. See page 12 of the Response.

Applicants argue that a *prima facie* case of obviousness has not been properly set because the Examiner has combined two references with opposing teachings. Applicants argue that one of ordinary skill in the art when combining the art of Thomson, who teach generating normal ESC lines from IVF embryos, and Harper, who teach away from using human embryos which carry genetic modifications, in further view of the '659 patent, which merely teaches methods of differentiating ES cells, or Elsea, who merely state that there is a need for human ESCs as a model for genetic modification, would not have any motivation or expectation of success to generate a human ES cell with a naturally occurring disease-casing mutation, methods of using the same. See page 12 of the Response.

Response to Arguments. These arguments have been considered but are not persuasive. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, Thomson is provided as guidance to show that human ES cell lines can be predictably and routinely made using human embryos. Harper provides guidance to show that the skilled artisan would readily have the skills and knowledge to identify human embryos which have a particular, naturally occurring disease-causing genetic mutation. Thus, these two references provide guidance for 1) producing human ES cell lines and 2) identification of particular mutations in human embryos. Elsea provides specific motivation to utilize embryos which have

specific mutations in order to establish human ES cell lines because the existing mouse ES cell lines fail to recapitulate human disease.

Applicants' Arguments/Response to Arguments. Applicants provide various secondary considerations in response to the rejection. See page 13 of the Response.

1-2. Long Felt but Unresolved Need/Unmet need. Applicants argue that Elsea establish the long felt need to generate the claimed cells because they teach that various mouse models of human diseases such as metachromatic leukodystrophy do not produce a biochemical model that reproduces clinical symptoms. Thus, long felt need has been recognized by those of skill in the art (*i.e.*, objective evidence) and not only by the present inventors. These arguments have been considered but are not persuasive. Elsea provide *motivation* to make the claimed invention. A long-felt need requires objective evidence that an art-recognized problem existed in the art for a long period of time without solution (see also, ¶716.04(I)). Elsea does not state that it is not possible, or that there is no solution to produce human ES cells with a particular disease-carrying mutation, in fact they provide guidance and suggestion to develop human ES cells. The art-recognized problem identified by Elsea is that mouse ES cells do not always reproduce human diseases, not that there was no solution or that it was not possible to produce isolated human ES cell lines with a naturally occurring disease causing mutation. Applicants further argue that the long felt need has not been satisfied by others before the invention by Applicants because there was no study which teaches or suggests using human embryos with naturally occurring disease causing mutations for establishing human ES cell lines. These arguments are not persuasive. In particular, it is noted that MPEP §716.04(II) states that a long-felt need is analyzed as of the date of the problem identified and articulated, and there is evidence of efforts to solve that problem, not as of the date of the most pertinent art reference. In the instant case, Elsea do not identify a problem with producing hES cell lines with a naturally occurring disease mutation, they identify a problem

with mouse ES cells, and thus provide suggestion and motivation to produce the hES cells and methods of the claimed invention. There is no evidence to show that there were other efforts (*i.e.*, other that Applicant's solution) made to solve this problem, and Applicants' citation of Elsea is not within the scope of Applicants' arguments.

3. Invention has satisfied the long felt need. Applicants argue that the present inventors generated various hESC lines which carry naturally occurring disease-causing mutations for studying various disease, and in addition, based upon the present teachings, multiple scientific studies have repeated the success of the present inventors by generation of additional hESC lines. These arguments have been considered but are not persuasive. As stated above, the prior art provides sufficient guidance, teachings and motivation to arrive at the claimed invention. In particular, Applicants' argument regarding long-felt need has been addressed above. Thus, arguing that the invention has satisfied this asserted long felt need is not persuasive because Applicants have not established that production of human ESC lines carrying a naturally occurring disease-causing mutation is a long-felt need in the art, wherein there is evidence to identify, articulate and solve this problem, prior to Applicants' invention.

4. Copying of the invention by competitors. Applicants point out that Stemride currently sells human ESC line carrying disease-causing mutations as taught and described by the present claims, and that the establishment of such an hESC line bank indicates that a substantial investment was made with the at least anticipated commercial success. These arguments are not found to be persuasive. MPEP §716.06 states: However, more than the mere fact of copying is necessary to make that action significant because copying may be attributable to other factors such as a lack of concern for patent property or contempt for the patentees ability to enforce the patent. *Cable Electric Products, Inc. v. Genmark, Inc.*, 770 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985). Evidence of copying was persuasive of

nonobviousness when an alleged infringer tried for a substantial length of time to design a product or process similar to the claimed invention, but failed and then copied the claimed invention instead. *Dow Chem. Co. v. American Cyanamid Co.*, **>816 F.2d 617<, 2 USPQ2d 1350 (Fed. Cir. 1987). Alleged copying is not persuasive of nonobviousness when the copy is not identical to the claimed product, and the other manufacturer had not expended great effort to develop its own solution. There is no guidance or evidence that Stemride did not expend great effort to develop its own solution, independent to Applicants' invention, and thus, copied the invention as instantly claimed.

Rejection

Thomson teach human embryonic stem cells from IVF embryos, and teach that genetic modifications could be produced in ES cells, for reducing or combating immune rejection (p. 1147, 1st col). Thomson further teach the production of cell lines from the human ES cells. Thomson teach that human ES cells can be differentiated by allowing the cells to grow to confluence and pile up (production of embryoid bodies, see p. 1146, col. 1, 2nd ¶). Additionally, Thomson teach that human ES cells would be valuable in studies of development and function of tissues that differ between mice and humans, and that screens based upon the *in vitro* differentiation to specific lineages could identify gene targets for new drugs (see p. 1146, col. 2-3, bridging ¶).

Thomson do not specifically teach that the embryos used would have a naturally occurring disease mutation. However, prior to the time of filing, screening of human embryos produced by IVF for various diseases was known in the art. Harper teaches that diseases, such as cystic fibrosis, Lesch Nyhan, Fragile X, Duchenne Muscular Dystrophy, Tay Sachs, haemophilia, can be done by PCR (see p. 1, Materials and Methods. See also pages 91-92, bridging paragraph and Table II. Thus, Harper provides methods in which to identify specific human IVF embryos

that have a naturally occurring disease causing mutation in a disease polypeptide, using PCR.

Neither Thomson nor Harper specifically teach the *in vitro* assay steps required by the claims. However, prior to the time of filing, the '659 document teaches methods for identifying candidate agents for treating conditions associated with motor neuron degeneration by obtaining embryonic stem cells, wherein the stem cells contain a mutation in a specific gene, contacting the ES cells with retinoic acid to differentiate the cells into neural progenitor cells, and determining the effect of an agent for use in treatment of a condition associated with motor neuron degeneration. See claim 1.

Given the teachings of Thomson and Harper, one of skill in the art would be able to use the methods of screening human embryos for a specific disease-causing mutation, and use those embryos in the methods taught by Thomson, in order to produce isolated human ES cell lines with a naturally occurring disease-causing mutation, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make these types of ES cells in order to use them in *in vitro* assays for identification of targets for new drugs (as suggested by Thomson), or to analyze the molecular mechanisms of the disease by allowing the ES cells to differentiate. Additionally, it would be obvious to utilize the resultant cells in methods of screening agents suitable for treating a disorder, such as the methods taught by the '659 document, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of Thomson's teachings who suggest producing genetic modifications in ES cells, and that human ES cells could be used for screening methods *in vitro* and the '659 document provide guidance with regard to the specific steps. Additionally, Elsea provide further guidance to show that various mouse models of human diseases, such as metachromatic leukodystrophy, do not produce a biochemical model that reproduces clinical symptoms (see Abstract) and therefore

show a need in the art to produce cells that could be used for screening various human diseases using human cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 82-84, 96-98 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* (**Science**, 282: 1145-1147, November 6, 1998) in view of Harper (**J. of Assisted Reproduction and Genetics**, 13(2): 90-95, 1996) in further view of US Pat. No. 7,390,659 (Issued June 24, 2008, cited previously) and Elsea *et al.* (**ILAR Journal**, 43(2): 66-79, 2002, cited previously) as applied to claims 52, 55, 58-60, 74, 75, 78-80, 85, 86, 88-94, 99, 100 and 101 above, and further in view of PGPub US 2005/0054092 A1.

Applicants have provided the same arguments, which have been responded to above.

Rejection

Thomson, Harper, the '659 patent and Elsea are described above. They do not specifically teach isolating lineage specific cells by mechanical separation of cells tissues and/or tissue-like structures contained within the embryoid body. However, prior to the time of the claimed invention, the '092 document teaches that suspensions of pPS derived cells can be further enriched with desirable characteristics, such as mechanical separation or cell sorting (p. 8, ¶117). In particular, the '092 document teaches that FACS sorting can be used (p. 10, ¶144).

Accordingly, it would have been obvious for one of skill in the art to modify the methods taught by Thomson, Harper and Elsea, to include a step of isolating a lineage-specific cell, utilizing either cell sorting, such as FACS sorting, or mechanical isolation techniques, as taught by the '092 document with a reasonable expectation of success. One of ordinary skill in the art would have been motivated

to make this modification in order to have a purified population of cells for *in vitro* screening assays.

Claims 57, 81, 87, 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* (**Science**, 282: 1145-1147, November 6, 1998) in view of Harper (**J. of Assisted Reproduction and Genetics**, 13(2): 90-95, 1996) in further view of US Pat. No. 7,390,659 (Issued June 24, 2008, cited previously) and Elsea *et al.* (**ILAR Journal**, 43(2): 66-79, 2002, cited previously) as applied to claims 52, 55, 58-60, 74, 75, 78-80, 85, 86, 88-94, 99, 100 above, and further in view of US Pat. No. 5,972,955.

Applicants have provided the same arguments, which have been responded to above.

Rejection

Thomson, Harper, the '659 patent and Elsea are described above. They do not specifically teach a sequence, such as those recited in claims 57, 81, 87 and 95. However, prior to the time of filing, the '995 reference teaches an exact match of SEQ ID NO: 24 (see alignment, presented previously).

Accordingly, it would have been obvious for the ordinary skilled artisan to modify the teachings of Thomson, Harper and Elsea, to screen for human embryos for a specific mutation, such as the W1282X as set forth in SEQ ID NO: 24, associated with cystic fibrosis, and use that embryo to produce an ES cell line, with a reasonable expectation of success. One of ordinary skill would have been motivated to make this modification in order to produce ES cells that could then be used for screen therapeutic agents for treatment of cystic fibrosis.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632